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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CELSA, BENNETT M

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 05/06/2002 12

Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary

Application No.	Applicant(s)
09/579,894	Saskela et al.
Examiner	**Art Unit**
Bennett Celsa	1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *9/17 and 9/26 2001 (amendment and supplemenal amendment)* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above, claim(s) *5-16* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4 and 17-19* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☒ Interview Summary (PTO-413) Paper No(s). *12*
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

Applicant's amendment (dated 2/19/02 in paper no. 8) and supplemental amendment (dated 9/26/01 in paper no. 9) adding new claims 17-19 and providing a copy of the provisional application (60/136,085 published 5/26/99) is hereby acknowledged.

Applicant's response (dated 2/19/02 in paper no. 11) electing the VSWSPD peptide, with traverse is acknowledged. Upon further consideration the election of species requirement (dated 12/18/01 in paper no. 10) is hereby withdrawn.

Status of the Claims

Claims 1-19 are currently pending.

Claims 1-4 and 17-19 are under consideration.

Claims 5-16 are withdrawn from consideration as being directed to nonelected subject matter. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Objection (s) and/or Rejection (s)

The nonenablement rejection over claims 1-4 is hereby withdrawn in view of applicant's arguments.

The indefinite rejection of claim 1 for use of the term "novel" and "tailored" is hereby withdrawn in view of applicant's amendment deleting this terminology.

The indefinite rejection of claim 1 regarding the lack of a difference between steps A and B upon further consideration, is hereby withdrawn.

The indefinite rejection of claim 2 over the term "effected" is withdrawn in view of applicant's amendment deleting this term.

The indefinite rejection of claim 2 for lack of antecedent basis of the term "the variable region" is withdrawn in view of applicant's amendment.

The indefinite rejections of claim 2 for lack of antecedent basis of the term "the six amino acid residues ..." and for use of the term "corresponding" are withdrawn in view of applicant's amendment.

The indefinite rejection of claim 4, upon further consideration, is withdrawn.

The anticipation rejection of claims 1-4 over the Hiipakka et al. J. Mol. Biol. Article has been overcome by applicant argument and the submission of the provisional application perfecting 119(e) priority; thus antedating the reference.

Outstanding Objection(s) and/or Rejection (s)

Claim Rejections - 35 USC § 112

2. Claims 1-4 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1 (and claims dependent thereon), "Step C is indefinite in the selection process to identify novel SH3 domains. The preamble recites generating not identifying any SH3 domains." Applicant's amendment reciting only "generating" does not obviate indefiniteness since the method clearly is addressing both a "generating" *and an identification step* (e.g. a screening step) in light of the preamble (e.g. "desired ligand binding properties ... ") and screening step present in step c) (e.g. "subjecting libraries *to affinity or function selection steps* ..." with emphasis). Amending the preamble to recite "and screening the domains for desired ligand binding properties" and amending step C by changing "generated" (as amended) to --- identified --- will overcome this rejection (since the pool of artificial SH3 domains already have been generated by steps a) and b).

Discussion

Applicant's amendment and argument directed to the above indefinite rejection was considered but deemed nonpersuasive for the following reasons. The above indefinite rejection has been revised in order to conform to applicant's amendment.

Applicant argues that the previous indefinite rejection is overcome through amendment.

However, as discussed in the revised rejection above, applicant's amended claim is still indefinite.

Accordingly, the above revised indefinite rejection is hereby retained.

3. Claims 1- 4 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lee et al. Embo J. Vol. 14, No. 20 pages 5006-5015 (1995)..

Lee et al. discloses a method of producing SH3 domains from the RT-loop region of different SH3 domains (e.g. from different SH3-kinases) . Lee produces said SH3 domains by first mutating some residues of the RT-loop of the different SH3 domains, e.g. page 5010, Fig. 4. The collection of mutant RT-loop region is obtained from a library of cDNA. "DNA fragments encoding" SH3 domains containing a "randomized RT-loop (RRT-SH3 domains)" are taught by the reference e.g. by use of cDNA encoding the kinase (e.g .human Hck) and polymerase chain reaction (e.g. amplification using primers) with "cloning" utilizing a "plasmid *vector*" to generate the recombinant library (e.g. see Lee et al. page 5013, right column). The RT-loop mutated region is then affinity purified to identify the mutant RT-loop peptide that binds to the PXXP motif of e.g., Nef with specificity and affinity; as well as the binding of the other "artificial" SH3 domains to their "desired ligands". In this regard the reference discloses "randomized" substitutions (one or a *combination e.g. 2, 3*) of amino acid substitutions within the RT loop, and specifically within non-conserved (e.g. "variable" regions), and *preferably*

including one or more substitutions (e.g. within a specific kinase or among a library of kinases) within a span which "*comprise* six amino acids that immediately follow a conserved stretch of amino acids having an ALYDY consensus sequence". (See e.g. Fig. 4 teaching both conserved and non-conserved amino acids of the RT-loop of kinases and Table I teaching the construction of a library (e.g a collection) of different kinases having "artificial SH3 domains having desired ligand binding properties" "comprising randomized RT-loops" wherein the collection of SH3 domains contain one or more "random" amino acid substitutions that comprise a hexapeptide sequence "that immediately follows a conserved stretch of amino acids having an ALYDY" (e.g. ...**(AL) YDY** hexapeptide DLS ...). With respect to SH3 binding and specificity (e.g. w/r to differential binding of SH3 containing kinases e.g. Hck and Fyn) to HIV-I, the Lee reference teaches that **"distinct specificity lies in a variable loop, the 'RT loop', positioned close to conserved SH3 residues implicated in the binding of proline-rich (PXXP) motifs" (emphasis provided)** . See ABSTRACT. It is considered that the different mutations of the different SH3 regions of the different kinases is the same to the claimed randomized RT-loop domains or would have been obvious to make into a random collections in view of the Lee's disclosure as to the different amino acids that can be mutated in the different SH3 domains of the SH3 wild type, particularly within the non-conserved regions of the RT-loop motif.

Discussion

Applicant's amendment and argument relating to the above 102/103 rejection was considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above 102/103 rejection was modified in order to address the newly amended claim limitations.

Applicant argues that "[I]n Lee et al. the RT-loop of Fyn-SH3 was modified to resemble the Hck-SH3. Thus, Lee et al. do not disclose the generation of randomized new sequences for RT-loop domains, rather they simply replace the RT-loop of Fyn-SH3 with another naturally occurring RT-loop sequence, that of Hck-SH3."

This argument is not found persuasive for several reasons.

First, the Lee et al. reference is not limited to one mutant SH3 domain (e.g. the Fyn SH3 mutant referred to by applicant) but extends to the making of multiple SH3 kinase domains containing multiple mutant RT-loop w/n non-conserved regions. Applicant has thus failed to appreciate the Lee reference teaching as a whole.

Secondly, the making of a mutant SH3 which *differs from the wild SH3 region* of a kinase would constitute a "new sequence" for one or more RT-loop domains as taught by the reference.

Thirdly, as pointed out in the 102/103 rejection above, the Lee reference clearly teaches (e.g. through example) and suggests (e.g. through explicit statements: e.g. see abstract) the making of artificial (e.g. differing from the wild type) SH3 domains of different kinase that contain random (e.g one or more amino acid substitutions) within the non-conserved regions (particularly a hexapeptide region) of the RT-loop region.

Applicant argues (citing specification discussion on page 5, lines 6-21) that "the present inventors have found that by using the presently recited method of random generation of the RT-loop sequence combined with affinity selection, instead of merely mimicking known SH3 domains, one can generate SH3 domains with specifically desired binding properties, such as unnaturally high affinity for specific proteins. Applicant further argues that there is no disclosure or suggestion in Lee et al. of a means of generating any but naturally occurring SH3 binding domains or of a method of generating artificial SH3 domains having desired binding properties.

Applicant's argument is not persuasive since it fails to appreciate both the specific teaching of the Lee et al. reference (through its examples) and the Lee reference teaching taken as a whole. As recited in the 102/103 rejection, the Lee et al. reference provides means for making SH3 domains (e.g. recombinant libraries employing cDNA, PCR, mutagenesis and recombinant libraries using plasmid cloning) and screening for desired (e.g. ligand- binding) clones; which SH3 domains are "artificial" by differing from the wild type due by one or more amino acid substitutions in the non-conserved portion (e.g. variable region) of the RT loop for one or more SH3 kinases.

Accordingly, the above revised 102/103 rejection, as modified, is hereby maintained.

New Objection (s) and/or Rejection

Claim Rejections - 35 USC § 112

4. Claims 17-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (NEW MATTER REJECTION)..

The specification and original claims (e.g. claims 7-9) only provide support for artificial SH3 domains which are derived from Hck-SH3 and targeted to the HIV-I Nef protein that contain the peptide motifs present in newly added claims 17-19. The original specification does not provide support for SH3 kinases and ligands beyond Hck and HIV-1 Nef protein. Applicant's must cancel the new matter in response to this rejection.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-4 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. Embo J. Vol. 14, No. 20 pages 5006-5015 (1995) and Sparks et al. J. Biol. Chem. Vol. 269, No. 39 (9/1994) pages 23853-23856.

Lee et al. disclose a method of producing artificial SH3 domains of different SH3-kinases, which differ by one or more amino acid substitutions in the non-conserved (e.g. variable) RT-loop region . Lee produces said SH3 domains by first mutating some residues of the RT-loop of the different SH3 domains, e.g. page 5010, Fig. 4. The collection of mutant RT-loop region is obtained from a library of cDNA. "DNA fragments encoding" SH3 domains containing a "randomized RT-loop (RRT-SH3 domains)" are taught by the reference e.g. by use of cDNA encoding the kinase (e.g .human Hck) and polymerase chain reaction (e.g. amplification using primers with "cloning" utilizing a "plasmid *vector*" to generate the library (e.g. see Lee et al. page 5013, right column). The RT-loop mutated region is then affinity purified to identify the mutant RT-loop peptide that binds to the PXXP motif of e.g., Nef with specificity and affinity; as well as the binding of other "artificial" SH3 domains to their "desired ligands". In this regard the reference discloses "randomized" substitutions (one or a *combination e.g. 2, 3*) of amino acid substitutions within the RT loop, and specifically within non-conserved (e.g. "variable" regions), and *preferably* including one or more substitutions (e.g. within a

specific kinase or among a library of kinases) within a span which "*comprise* six amino acids that immediately follow a conserved stretch of amino acids having an ALYDY consensus sequence". (See e.g. Fig. 4 teaching conserved/ non-conserved amino acids of aligned SH3 kinase RT-loops; and Table I teaching the construction of a collection of different kinases having "artificial SH3 domains having desired ligand binding properties" "comprising randomized RT-loops" wherein the collection of SH3 domains contain one or more "random" amino acid substitutions that comprise a hexapeptide sequence "that immediately follows a conserved stretch of amino acids having an ALYDY" (e.g. ...**(AL) YDY** hexapeptide DLS ...). With respect to SH3 binding and specificity (e.g. w/r to differential binding of SH3 containing kinases e.g. Hck and Fyn) to HIV-I, **"distinct specificity lies in a variable loop, the 'RT loop', positioned close to conserved SH3 residues implicated in the binding of proline-rich (PXXP) motifs" (emphasis provided)** . See ABSTRACT.

The Lee et al. reference teaching differs from the presently claimed invention (e.g. new claims 17-19) since it fails to explicitly teach generating "artificial Hck-SH3" libraries by randomizing (e.g. with all 20 natural amino acids) the non-conserved hexapeptide 69-74 (EAIHHE) RT-loop sequence of Hck (or related SH3 kinases) to obtain completely random libraries comprising 20^6 (e.g. 20x20x20x20x20x20) artificial Hck-SH3 proteins differing from the wild type at hexapeptide 69-74 (EAIHHE) for subsequent ligand screening (e.g. with HIV-I Nef) and selection of artificial Hck-SH3 proteins containing "optimum" motifs.

However, the Lee et al. reference further teaches that HIV-I Nef protein binds to the SH3 domains of a subset of Src family kinases (including Hck and Fyn); and the SH3 binding capacity of Nef is necessary for optimal spread of HIV-I infection (e.g. via replication). Accordingly, blocking the interaction (e.g. via use of competitive inhibitors) between the HIV-Nef protein and the Src family kinases (e.g. Hck and Fyn) may be therapeutic for HIV infection. See e.g. page 5006 right column to page 5007. The Lee et al .reference further teaches that, w/r to specificity and binding of HIV-I Nef protein to the SH3 domain of Src family kinases, "distinct specificity lies in a variable loop, the 'RT loop', positioned close to conserved SH3 residues implicated in the binding of proline-rich (PXXP) motifs" e.g. at hexapeptide 69-74 (EAIHHE) non-conserved peptide region of Hck (and the corresponding position w/r to the other Src family kinases); and thus the development of artificial SH3 protein analogs which preferentially bind the HIV-I Nef protein may be therapeutic in preventing HIV infection. E. g. See abstract; and page 5013.

Accordingly, the Lee et al. reference provides motivation to one of ordinary skill in the art to make recombinant libraries (using the Lee reference method) that comprise randomization of the non-conserved (e.g. variable) RT loop hexapeptide 69-74 (EAIHHE) peptide sequence of Hck or the corresponding region in other Src family kinases in order to screen such libraries for potential competitive inhibitors useful in treating HIV infection. One would be motivated to completely randomize the hexapeptide variable RT loop region in order to obtain the largest possible library (e.g. a completely random library comprising 20^6 (e.g. 20x20x20x20x20x20)

artificial Hck-SH3 proteins or other artificial Src family kinase proteins) for screening and thus *optimizing* the likelihood of finding therapeutically useful competitive inhibitors.

Thus, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention, in light of the Lee reference teaching alone, to generate "artificial Hck-SH3" peptide (or other Src family kinase peptide) libraries by randomizing (e.g. with all 20 natural amino acids) a hexapeptide 69-74 (EAIHHE) of Hck (or the corresponding region of a related Src family protease) to obtain a complete random library comprising 20^6 artificial Hck-SH3 proteins differing from the wild type at hexapeptide 69-74 (EAIHHE) since the Lee reference suggests the making of competitive inhibitors of HIV infection by modifying the amino acids in the variable hexapeptide (69-74) region of Hck (or other Src family kinases) to generate inhibitors. Additionally, the making of the largest library (e.g by complete randomization of each amino acid) for screening potential HIV-I inhibitors represents mere optimization.

Additionally, the Sparks et al. reference teaches the utilization of "biased peptide libraries" or , preferentially "random peptide libraries" (e.g. all 20 amino acids), including 7mer/8mer peptide libraries, via phage display, as a means for making and screening Src SH3 ligands for developing "antagonists of Src SH3 interactions with SH3-binding proteins" . See abstract; and entire article.

Accordingly, the Sparks et al. reference provides further motivation to make and screen "random peptide libraries" for developing "antagonists of Src SH3 interactions with SH3-binding proteins" which can be useful to treat HIV infection.

Thus, it would have been obvious to one of ordinary skill in the art, in view of the combined teaching of the Lee and Sparks references, to generate "artificial Hck-SH3" (or other Src family kinase proteins) libraries by making "random peptide libraries" comprising the hexapeptide 69-74 (EAIHHE) peptide sequence (or corresponding sequence) to obtain a complete random library, using either the Lee (recombinant) or Sparks (phage display) method of library generation in order to screen for potential HIV therapeutics..

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

May 2, 2002

BENNETT CELSA
PRIMARY EXAMINER